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Lymphomas

ECM–DLBCL INTERACTIONS DRIVE REVERSIBLE IBRUTINIB RESISTANCE IN A 3D BONE MODEL

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Introduction: Diffuse large B-cell lymphoma (DLBCL) frequently relapses after therapy, partly due to microenvironment-mediated resistance. Protective interactions between lymphoma cells and the bone marrow extracellular matrix (ECM) sustain survival and drug tolerance, whereas conventional 2D cultures fail to reproduce these cues. To better model this context, we established a human bone-derived decellularized scaffold preserving the native architecture of the bone marrow niche. This 3D system enables the study of DLBCL-ECM interactions and resistance mechanisms in a physiological relevant setting.

Methods Four DLBCL cell lines (OLI-LY1, OCI-LY18, RIVA, NU-DUL-1) were cultured on bone-derived 3D ECM scaffolds to assess proliferation, cytokine secretion, and ibrutinib sensitivity. Cell motility was evaluated by transwell migration and scaffold colonization assays. Cytokine profiles from 2D and 3D cultures were analyzed by array, PCA and STRING network modeling. PDMS scaffolds served as non-biological 3D controls.

Results: PCA showed distinct cytokine patterns between 2D and 3D cultures. STRING analysis of upregulated cytokines identified a strongly interconnected chemokine cluster ($p < 10^{-16}$) involved in leukocyte migration and chemokine-mediated signaling. OCI-LY18 DLBCL cells displayed enhanced migration toward conditioned media and 3D scaffolds ($p<0.005$), and scaffold colonization increased when pre-seeded with lymphoma cells (n=3-6, $p<0.05$). All cell lines underwent significant apoptosis after ibrutinib in 2D (n=3, $p<0.005$) whereas OCI-LY18 and RIVA cells showed reduced apoptosis in 3D ($p< 0.005$). When re-expanded in 2D, these cells regained ibrutinib sensitivity, indicating reversible, ECM-dependent resistance. Preliminary data suggest activation of AKT/mTOR pathway in 3D conditions. This phenotype appeared to be independent of DLBCL subtype.

Conclusions: The bone-derived 3D model recapitulates a biologically faithful bone marrow niche for DLBCL. ECM interactions transiently confer ibrutinib resistance and reshape cytokine secretion, possibly through AKT/mTOR signaling. This *ex-vivo* platform provides a valuable preclinical tool to dissect microenvironment-driven resistance, and to support personalized therapeutic in bone-infiltrating DLBCL.